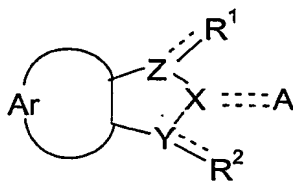


Patent claims

1. A compound according to the general formula



(I)

wherein the dotted lines denote a single bond which is optionally present, with 1 dotted line and 1 full line or 2 dotted lines denoting a double bond; wherein, in case no double bond is present and a free valence exists, this valence is occupied by H; and wherein the symbols have the following meanings:

R^1 and R^2 are independently from each other selected from the group consisting of: H; (=O); OH; OSO_3^- ; halogens; pseudohalogens; NR^3R^4 ; $\text{S(O)}_m\text{R}^5$; $\text{SO}_2\text{NR}^6\text{R}^7$; C(O)R^8 ; C(O)OR^9 ; $\text{CONR}^{10}\text{R}^{11}$; substituted and unsubstituted $\text{C}_1\text{-C}_3$ -alkyl and substituted and unsubstituted $\text{C}_1\text{-C}_3$ -alkoxy, which alkyl and alkoxy groups, if substituted, carry at least one substituent from the group: OH, OSO_3^- , halogens, pseudohalogens, NR^3R^4 , $\text{S(O)}_m\text{R}^5$, $\text{SO}_2\text{NR}^6\text{R}^7$, C(O)R^8 , C(O)OR^9 , $\text{CONR}^{10}\text{R}^{11}$, and wherein at least one substituent is different from H;

Ar denotes a substituted or unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1, 2 or 3 heteroatoms from the group N, O and S in its cycle;

Y, Z denote independently from each other a nitrogen atom, an oxygen atom, a sulfur atom or a methylene group;

X is a nitrogen atom, an oxygen atom, a sulfur atom, or a methylene group;

A is selected from the group consisting of: H; halogens and pseudohalogens; OH; $=\text{N(OH)}$; $\text{NR}^{12}\text{R}^{13}$; OSO_3^- ; $\text{S(O)}_m\text{R}^{14}$; $\text{SO}_2\text{NR}^{15}\text{R}^{16}$; C(O)R^{17} ; C(O)OR^{18} ; $\text{CONR}^{19}\text{R}^{20}$; C(S)R^{21} ; C(S)OR^{22} ; unsubstituted and at least monosubstituted $\text{C}_1\text{-C}_{12}$ -alkyl which can carry in its chain one or more non-adjacent heteroatoms from the group nitrogen and oxygen, and which, if substituted, carry at least one substituent which is preferably selected from the group consisting of: halogens, pseudohalogens, OH, $\text{NR}^{12}\text{R}^{13}$, OSO_3^- , $\text{S(O)}_m\text{R}^{14}$, $\text{SO}_2\text{NR}^{15}\text{R}^{16}$, C(O)R^{17} , C(O)OR^{18} , $\text{CONR}^{19}\text{R}^{20}$, C(S)R^{21} , C(S)OR^{22} , and substituted and non-substituted aryl and substituted and non-

substituted heteroaryl which, if substituted, carry at least one substituent from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, pseudohalogens, and CF₃;

R³, R⁴ are independently selected from the group consisting of:

H; substituted and unsubstituted methyl and ethyl which, if substituted, can carry one or more substituents from the group OH, halogens, pseudohalogens,;

R⁵ independently has the same meaning as R³;

R⁶ and R⁷ independently have the same meaning as R³, R⁴;

R⁸ is H or C₁-C₃-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of OH, C(O)H, C(O)CH₃, C(O)C₂H₅, halogens, pseudohalogens, NH₂, mono(C₁-C₃-alkyl)amino, di(C₁-C₃-alkyl)amino;

R⁹ is H or C₁-C₃-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of OH, C(O)H, C(O)CH₃, C(O)C₂H₅, halogens, pseudohalogens, NH₂, mono(C₁-C₃-alkyl)amino, di(C₁-C₃-alkyl)amino;

R¹⁰, R¹¹ independently have the same meaning as R³, R⁴;

R¹², R¹³ independently are H or unsubstituted and at least monosubstituted C₁-C₁₂-alkyl which can carry in its chain one or more non-adjacent heteroatoms from the group nitrogen and oxygen, and which, if substituted, carry one or more substituents from the group consisting of: OH, C(O)H, C(O)CH₃, C(O)C₂H₅, halogens, pseudohalogens, NH₂, mono(C₁-C₃-alkyl)amino, di(C₁-C₃-alkyl)amino, and unsubstituted and at least monosubstituted aryl and heteroaryl, which, if substituted, carry at least one substituent from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, pseudohalogens, and CF₃;

R¹⁴ has the same meaning as R¹²

R¹⁵, R¹⁶ independently have the same meaning as R¹², R¹³;

R¹⁷ has the same meaning as R¹²;

R¹⁸ has the same meaning as R¹²

R¹⁹, R²⁰ independently have the same meaning as R¹², R¹³;

R²¹ has the same meaning as R¹²;

R²² has the same meaning as R¹²;

aryl is 5 to 10-membered, mono- or bicyclic aromatic cycle;

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

m is 1, 2 or 3,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein the symbols have the following meanings:

R^1 and R^2 are independently from each other selected from the group consisting of:

H; OH; (=O); halogens; pseudohalogens; NH_2 ; $S(O)_mR^5$; SO_2NH_2 ; $C(O)R^8$; $C(O)OR^9$; $CONH_2$; C_1 - C_2 -alkyl substituted by NH_2 , OH, $S(O)_mR^5$, SO_2NH_2 , $C(O)R^8$, $C(O)OR^9$, $CONH_2$; C_1 - C_2 -alkoxy substituted by NH_2 , OH, $S(O)_mR^5$, SO_2NH_2 , $C(O)R^8$, $C(O)OR^9$, $CONH_2$;

Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1, 2 or 3 heteroatoms from the group N, O and S in its cycle;

Y, Z denote independently from each other a nitrogen atom or a methylene group;

X is a nitrogen atom or a methylene group;

A is selected from the group consisting of: H; halogens and pseudohalogens; OH; $=N(OH)$; $NR^{12}R^{13}$; OSO_3^- ; $S(O)_mR^{14}$; $SO_2NR^{15}R^{16}$; $C(O)R^{17}$; $C(O)OR^{18}$; $CONR^{19}R^{20}$; $C(S)R^{21}$, $C(S)OR^{22}$; unsubstituted and at least monosubstituted C_1 - C_6 -alkyl which can carry in its chain one or more non-adjacent heteroatoms from the group nitrogen and oxygen, and which, if substituted, carry at least one substituent which is preferably selected from the group consisting of: halogens, pseudohalogens, OH, $NR^{12}R^{13}$, OSO_3^- , $S(O)_mR^{14}$, $SO_2NR^{15}R^{16}$, $C(O)R^{17}$, $C(O)OR^{18}$, $CONR^{19}R^{20}$, $C(S)R^{21}$, $C(S)OR^{22}$, and substituted and non-substituted aryl and substituted and non-substituted heteroaryl which, if substituted, carry at least one substituent from the group consisting of C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, halogens, pseudohalogens, and CF_3 ;

R^5 is selected from H; substituted and unsubstituted methyl and ethyl which, if substituted, can carry one or more substituents from the group OH, halogens, pseudohalogens,;

R^8 is H or C_1 - C_3 -alkyl which can be unsubstituted or carry one or more substituents from the group consisting of OH, $C(O)H$, $C(O)CH_3$, $C(O)C_2H_5$, halogens, pseudohalogens; NH_2 , mono(C_1 - C_3 -alkyl)amino, di(C_1 - C_3 -alkyl)amino;

R^9 is H or C_1 - C_3 -alkyl which can be unsubstituted or carry one or more substituents from the group consisting of OH, $C(O)H$, $C(O)CH_3$, $C(O)C_2H_5$, halogens, pseudohalogens; NH_2 , mono(C_1 - C_3 -alkyl)amino, di(C_1 - C_3 -alkyl)amino;

R^{12} , R^{13} independently are H or unsubstituted and at least monosubstituted C_1 - C_{12} -alkyl which can carry in its chain one or more non-adjacent heteroatoms from the group nitrogen and oxygen, and which, if substituted, carry one or more substituents from the group consisting of: OH, $C(O)H$, $C(O)CH_3$, $C(O)C_2H_5$, halogens, pseudohalogens, NH_2 , mono(C_1 - C_3 -alkyl)amino, di(C_1 - C_3 -alkyl)amino, and

unsubstituted and at least monosubstituted aryl and heteroaryl, which, if substituted, carry at least one substituent from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, pseudohalogens, and CF₃;

R¹⁴ has the same meaning as R¹²

R¹⁵, R¹⁶ independently have the same meaning as R¹², R¹³;

R¹⁷ has the same meaning as R¹²;

R¹⁸ has the same meaning as R¹²

R¹⁹, R²⁰ independently have the same meaning as R¹², R¹³;

R²¹ has the same meaning as R¹²;

R²² has the same meaning as R¹²;

aryl is phenyl, naphth-1-yl or naphth-2-yl

heteroaryl is selected from the group consisting of 5- and 6- membered monocyclic and 9- or 10-membered bicyclic heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

m is 1, 2 or 3

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein the symbols have the following meanings:

R¹ and R² are independently from each other selected from the group consisting of:

H; OH; (=O); halogens; pseudohalogens; with at least one of R¹, R² being (=O);

Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1 or 2 heteroatoms from the group N, O and S in its cycle;

Y, Z denote independently from each other a nitrogen atom or a methylene group;

X is a nitrogen atom or a methylene group;

A is an at least monosubstituted C₁-C₃-alkyl having a H-atom in position α to X, which alkyl can carry in its chain one or more non-adjacent heteroatoms from the group nitrogen and oxygen, wherein the at least one substituent is selected from the group consisting of: C(O)R¹⁷, C(O)OR¹⁸, and substituted and non-substituted aryl and substituted and non-substituted heteroaryl which aryl and heteroaryl, if substituted, carry at least one substituent from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, pseudohalogens, and CF₃;

R¹⁷ is selected from H and unsubstituted C₁-C₃-alkyl;

R¹⁸ has the same meaning as R¹⁷;

aryl is phenyl, naphth-1-yl or naphth-2-yl;

heteroaryl is selected from the group consisting of indolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

4. A compound according to claim 3, wherein the symbols have the following

5 meanings:

R^1 and R^2 are independently from each other selected from the group consisting of:
H; (=O); with at least one of R^1 , R^2 being (=O), preferably both being (=O);

10 Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1 or 2 nitrogen atoms in its cycle;

Y, Z denote independently from each other a nitrogen atom or a methylene group, preferably Y, Z are both methylene;

X is a nitrogen atom or a methylene group, preferably X is a nitrogen atom;

15 A is an at least bisubstituted C_1 - C_3 -alkyl having a H-atom in position α to X, wherein the at least two substituents are selected from the group consisting of: $C(O)OR^{18}$, and substituted and non-substituted aryl and substituted and non-substituted heteroaryl which aryl and heteroaryl, if substituted, carry at least one substituent from the group consisting of C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, halogens, pseudohalogens, and CF_3 ;

R^{18} is selected from H and unsubstituted C_1 - C_3 -alkyl;

20 aryl is phenyl, naphth-1-yl or naphth-2-yl;

heteroaryl is selected from the group consisting of indolyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

- 25 5. A compound according to claim 4, wherein the symbols have the following meanings:

R^1 and R^2 are both (=O);

30 Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1 nitrogen atom in its cycle;

Y, Z are both methylene;

X is a nitrogen atom;

35 A is a bisubstituted C_1 - C_3 -alkyl having a H-atom in position α to X, wherein one substituent is selected from the group consisting of $C(O)OR^{18}$, and the other substituent is selected from substituted and non-substituted aryl and substituted and non-substituted heteroaryl which aryl and heteroaryl, if substituted, carry at least one

substituent from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, pseudohalogens, and CF₃;

R¹⁸ is selected from H and unsubstituted C₁-C₃-alkyl;

aryl is phenyl, naphth-1-yl or naphth-2-yl;

5 heteroaryl is indolyl.

6. A compound according to claim 5, wherein the symbols have the following meanings:

R¹ and R² are independently from each other selected from the group consisting of:

10 H; (=O); with at least one of R¹, R² being (=O), preferably both being (=O);

Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1 or 2 nitrogen atoms in its cycle;

15 Y, Z denote independently from each other a nitrogen atom or a methylene group, preferably Y, Z are both methylene;

X is a nitrogen atom or a methylene group, preferably X is a nitrogen atom;

A is an at least monosubstituted C₁-C₃-alkyl having a H-atom in position α to X, wherein the at least one substituent is selected from the group consisting of: C(O)OR¹⁸, C(S)OR²²;

20 R¹⁸ is selected from H and unsubstituted C₁-C₃-alkyl;

R²² is selected from H and unsubstituted C₁-C₃-alkyl.

7. A compound according to claim 6, wherein the symbols have the following meanings:

25 R¹ and R² are both (=O);

Ar denotes an unsubstituted mononuclear aryl group having 6 or 7 members, which aryl group is annulated to the neighbouring 5-membered cycle, and which may carry 1 nitrogen atom in its cycle;

Y, Z are both methylene;

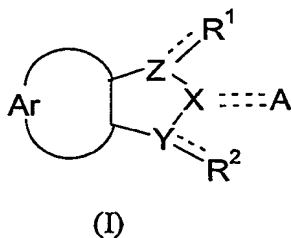
30 X is a nitrogen atom;

A is a monosubstituted C₁-C₃-alkyl having a H-atom in position α to X, wherein the substituent is C(O)OR¹⁸;

R¹⁸ is selected from H and unsubstituted C₁-C₃-alkyl.

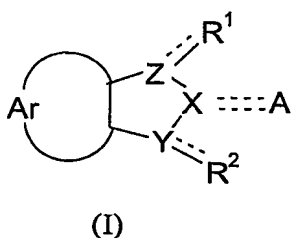
35

8. A compound according to the general formula (I)



5 wherein the symbols Ar, A, X, Y, and Z and the substituents R¹ and R² have the meaning defined in any of claim 1 to 7, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

9. The use of a compound of formula (I)



15 wherein the symbols Ar, A, X, Y, and Z and the substituents R¹ and R² have the meanings defined in any of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical for the inhibition of DNMTs, more particularly DNMT1, and/or the inhibition of DNA methylation.

10. The use according to claim 9, wherein the pharmaceutical is for the treatment of a disease associated with aberrant DNA methylation.

11. The use according to claim 10, wherein the disease is a developmental disorder or a proliferative disease.

12. The use according to claim 11, wherein the disease is Prader-Willi-Syndrome, Angelman-Syndrome (Happy Puppet Syndrome), Beckwith-Wiedemann-Syndrome, coronary restenosis, neuroblastoma, intestine carcinoma such as rectum carcinoma, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-

polyposis colorectal cancer, esophageal carcinoma, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, renal carcinoma, kidney parenchyma carcinoma, ovarian carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, pancreatic carcinoma, prostate carcinoma, testis carcinoma, breast carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), adult T-cell leukemia lymphoma, hepatocellular carcinoma, gall bladder carcinoma, bronchial carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroid melanoma, seminoma, rhabdomyosarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, prostate carcinoma, or plasmocytoma.

13. The use according to claim 12, wherein the disease is colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, prostate carcinoma, melanoma, non-Hodgkin lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), or hepatocellular carcinoma.

14. The use according to any of claims 9 to 13, wherein the disease is Prader-Willi Syndrome, Angelman Syndrome (Happy Puppet Syndrome), Beckwith-Wiedemann Syndrome.

15. The use according to any of claims 9 to 14, wherein the pharmaceutical is co-administered with a compound selected from the group consisting of (i) antimetabolites, cytarabine, fludarabine, 5-fluoro-2'-deoxyuridine, gemcitabine, hydroxyurea or methotrexate; (ii) DNA-fragmenting agents, bleomycin, (iii) DNA-crosslinking agents, chlorambucil, cisplatin, fotemustine, cyclophosphamide or nitrogen mustard; (iv) intercalating agents, adriamycin (doxorubicin) or mitoxantrone; (v) protein synthesis inhibitors, L-asparaginase, cycloheximide, puromycin or diphtheria toxin; (vi) topoisomerase I poisons, camptothecin or topotecan; (vii) topoisomerase II poisons, etoposide (VP-16) or teniposide; (viii) microtubule-directed agents, colcemid, colchicine, paclitaxel (taxol), docetaxel

(taxotere), vinblastine or vincristine; (ix) kinase inhibitors, flavopiridol, staurosporin, STI571 (CPG 57148B) or UCN-01 (7-hydroxystaurosporine); (x) miscellaneous investigational agents, trichostatin A, thioplatin, PS-341, phenylbutyrate, ET-18-OCH₃, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols, quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; (xi) hormones, glucocorticoids or fenretinide; (xii) hormone antagonists, tamoxifen, finasteride or LHRH antagonists, (xiii) demethylating agents, 5-azacytidine, 5-aza-2'deoxycytidine, 5,6-dihydro-5-azacytidine, or (xiv) a combination of any of the pharmaceuticals given above.

16. The use according to any of claims 9 to 15, wherein the pharmaceutical is for the induction of cellular differentiation.

17. The use according to any of claims 9 to 16, wherein the pharmaceutical is for the treatment of infections.

18. A pharmaceutical preparation comprising an effective dose of at least one compound of the formula (I) as defined in any of claims 1 to 7 and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.